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EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 01/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/513,362	CHEE ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *03112003*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. This office action is in response to an amendment filed November 3, 2003. Claims 1-32 were previously pending. Applicants amended claims 3-5, 10 and 11 and added new claims 33 and 34. Claims 1-34 are pending and will be examined.

2. Applicants' amendments overcame the following rejections: rejection of claims 3-5, 11, 12 and 25-27 under 35 U.S.C. 112, second paragraph. All other rejections are maintained for reasons given in the "Response to Arguments" section.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on November 3, 2003 was filed after the mailing date of the non-final office action on April 24, 2003. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Response to Arguments

4. Applicant's arguments filed November 3, 2003 have been fully considered but they are not persuasive.

A) Regarding rejection of claims 1-4, 6-10, 12-17 and 22-27 under 35 U.S.C. 103(a) over Navot et al. and Walt et al., Applicants argue that Navot et al. do not teach large scale sequence determination involving a plurality of target nucleic acids, and that there is no motivation to combine Navot et al. and Walt et al. However, as noted in the previous office action, there is a perfectly valid motivation to combine the two references. In this case, Navot et al. teach pyrosequencing of nucleic acids which may be attached to microbeads in an electrophoresis-free system, and attachment to the solid support provides confinement to the sample (col. 15, lines 1-14), and Walt et al. teach microbeads with attached nucleic acids, distributed randomly on the surface of

the fiber optic bundle, creating an microbead array (col. 3, lines 35-45; col. 4, lines 35-38; col. 8, lines 15-19; col. 9, lines 41-67; col. 10, lines 1-47). Both references teach microbeads, and Walt et al. teaches an efficient and inexpensive way of creating an array (col. 4, lines 53-58). Therefore, provided with the teachings of Navot et al. and Walt et al., a skilled artisan would be motivated to use the microbead array of Walt et al. to detect the microbead sequencing reactions of Navot et al. Further, the paragraph from Walt et al. cited by Aplicants (col. 4, lines 44-59) provides additional support for the motivation to use the references, since Walt et al. teach synthesis of bioactive agents, which is what DNA sequencing is.

The rejection is maintained.

B) Regarding rejection of claims 5 and 11 under 35 U.S.C. 103(a) over Navot et al., Walt et al. and Balch et al., Applicants argue that there is no motivation to combine the references. First, Balch et al. teach a Universal array for performing a multitude of molecular biology reactions. Such an array contains capture probes, which are attached to a solid support, and the probes contain sequences complementary to adapter probes, which bind to the target (col. 16, lines 65-67; col. 16, lines 1-37). In this way, the array can be manufactured with capture probes only, and customized by the user to detect specific target sequences by customizing the adapter probes. Therefore the statement that adapter probes provide unique binding sites is not merely conclusory, but expressly taught by Balch et al. In addition to the motivation provided by the above paragraph, of making cheaper small arrays by having only capture probes synthesized on solid support (col. 16, lines 60-64), Balch et al. provides additional motivation which would make it obvious for one of ordinary skill in the art to use adapter probe/capture probe complexes. For example, col. 22, lines 1-15, has the following statement (emphasis added):

"A specific example of the target probe domains that are cognate to the capture probe set of the Universal Array and can be modified to allow for direct binding to a specifically modified probe, nucleic acid or other molecule capable of selective binding to the analyte of interest is illustrated in FIG. 5b. FIG. 5b is a diagram showing direct binding for a target probe. As shown in FIG. 5b, the target probe is constructed from two parts; the first is a presynthesized probe (TP1) complementary to a capture probe which has a linkage element for attaching the second target complex (TP2). Such embodiment yields a high degree of simplicity for the customer since the first target component can be offered in a ready-to-use format."

Therefore, one of ordinary skill in the art would find ample motivation in Balch et al. to combine with Navot et al. and Walt et al.

The rejection is maintained.

C) Regarding rejection of claims 18-31 and 28-30 under 35 U.S.C. 103(a) over Navot et al., Walt et al. and Nyren et al., Applicants argue that there is no motivation to combine Navot et al. and Walt et al., and, further, no motivation exists to combine Nyren et al. with the two. Response to the first part of the argument is provided in part A). Further, both Navot et al. and Nyren et al. teach pyrosequencing and pyrosequencing kits, with Navot et al. teaching a kit comprising primers and DNA polymerase (col. 6, lines 63-67; col. 7, lines 1-10; col. 9, lines 5-7), and Nyren et al. teach a kit comprising a sequencing primer, a polymerase, a detection enzyme means for identifying pyrophosphate release, dNTPs or ddNTPs (page 20, second paragraph; page 21, first paragraph). Therefore, as can be seen from these two references, there is a strong motivation to combine different reaction components into kits. Since strong motivation exists to combine Walt et al. with Navot et al., it would have been obvious to add components of the array of Walt et al. to the kit.

The rejection is maintained.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-4, 6-10, 12-17, 22-27 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Navot et al. (U.S. Patent No. 6,335,165 B1; cited in the previous office action) and Walt et al. (U.S. Patent No. 6,327,410 B1; cited in the previous office action).

A) Navot et al. teach a method of sequencing GC-rich regions of nucleic acids, the method comprising contacting modified GC-rich nucleic acid with a sequencing primer, synthesizing a complementary strand in a stepwise manner, in which an identity of each incorporated nucleotide is determined, and determining the sequence of the GC-rich nucleic acid (col. 7, lines 10-29; col. 12, lines 34-46). The nucleotide addition is catalyzed by a DNA polymerase (the first enzyme) (col. 14, lines 46-67). Navot et al. teach amplification of genomic DNA (col. 6, lines 53-58; col. 18, lines 37-40).

The identity of each incorporated oligonucleotide can be determined by monitoring a release of a pyrophosphate (PPi) group and the detection of PPi is achieved enzymatically. The PPi formed in the sequencing reaction is converted to ATP by ATP sulfurylase (second enzyme) and the ATP production is monitored by the firefly luciferase (third enzyme) (col. 7, lines 60-67; col. 4, lines 55-67; col. 5, lines 1-36; col. 12, lines 66-67; col. 13, lines 1-35).

Another way of determining the identity of an incorporated nucleotide is achieved by using nucleotide analogs, which include a removable blocking group at the 3'-OH position and a

removable reporter group. Following the addition of a nucleotide to the complementary strand the blocking group is removed to permit the addition of the next nucleotide. The removable reporter group allows identification of the incorporated nucleotide (col. 13, lines 43-67).

The target nucleic acid can be bound to a solid support either directly or indirectly, for example, through a capture probe (col. 10, lines 29-33). In another embodiment, either the sequencing primer or the target can be immobilized on beads (col. 15, lines 1-14).

Navot et al. teach a kit comprising amplification primers and a DNA polymerase (col. 6, lines 63-67; col. 7, lines 1-10; col. 9, lines 5-7).

B) Navot et al. do not teach microspheres (beads) randomly distributed on a surface of a substrate, where the substrate comprises discrete sites, and the discrete sites are wells. They do not teach the substrate being a fiber optic bundle.

C) Walt et al. teach microsphere-based analytical chemistry system in which the microspheres are distributed on a substrate which might be a fiber optic bundle (Abstract). The surface of the substrate comprises discrete sites into which at least two subpopulations of microspheres are distributed. Each of the microspheres comprises a bioactive agent and an optical signature which allows identification of the bioactive agent. The beads can be randomly distributed on the array (col. 3, lines 35-45; col. 4, lines 35-58). The bioactive agent attached to the microsphere can be a nucleic acid, particularly a nucleic acid probe (col. 8, lines 15-19; col. 9, lines 41-67; col. 10, lines 1-47). The array can be used for sequencing (col. 24, lines 51-52).

The substrate materials include glass, plastics and a variety of other materials. The surface of the substrate contains discrete sites, which might be wells, and the substrate may be a fiber optic bundle (col. 5, lines 32-46, lines 61-67; col. 6, lines 22-41).

Walt et al also teach a composition comprising a substrate with discrete sites (wells) and a population of microspheres randomly distributed in the wells, the microspheres comprising a bioactive agent (claims 1, 5, 9, 27 and 39).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used microspheres randomly distributed on a substrate of Walt et al. as the beads in the pyrosequencing method of Navot et al. The motivation to do so, expressly provided by Walt et al., would have been that synthesis of nucleic acids was separated from their placement on the array and random distribution of beads was fast and inexpensive.

7. Claims 5, 11 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Navot et al. and Walt et al. as applied to claims 1 and 10 above, and further in view of Balch (U.S. Patent No. 6,083,763; cited in the previous office action).

A) Claim 5 is drawn to the hybridization complexes comprising target sequences, sequencing primers, adapter probes and capture probes covalently attached to the microspheres. Claim 11 is drawn to a hybridization complexes comprising capture probes. Claim 33 is drawn to a method of claim 11 where the hybridization complexes comprise adapter probes.

B) Neither Navot et al. nor Walt et al. teach adapter probes.

C) Balch teaches molecular analysis aparatus for high-throughput analysis of molecular targets in complex mixtures. This apparatus can be used for DNA amplification and sequencing in an array format. (Abstract, Example III). Each location of the array comprises a capture probe attached to a solid substrate (col. 17, lines 28-41; col. 18, lines 55-66). The target probes (adapter probes) are designed to be complementary to both the capture probes and the target nucleic acids (col. 20, lines 39-49; Fig. 5a). The capture probes can be used directly to form hybridization complexes with the target nucleic acid sequences (col. 21, lines 21-23).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the adapter probes of Balch for the formation of primer-target complexes in the combined method of Navot et al. and Walt et al. The motivation to do so, expressly provided by Balch, would have been that adapter probes a delivered unique binding domain for each site on an array.

8. Claims 18-21 and 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Navot et al. and Walt et al. as applied to claims 1 and 10 above, and further in view of Nyren et al. (WO 98/13523; cited in the previous office action).

A) Claims 18-21 are drawn to a kit for nucleic acid sequencing comprising a substrate with discrete sites, population of microspheres randomly distributed in these sites, the microspheres comprising capture probes, an extension enzyme, dNTPs, a second enzyme for conversion of PPi to ATP, a third enzyme for the detection of ATP, and dNTPs with different labels.

B) Navot et al. teach a kit as described above, but does not teach a substrate with discrete sites, population of microspheres randomly distributed in these sites, the microsphres comprising capture probes, dNTPs, a second enzyme for conversion of PPi to ATP, a third enzyme for the detection of ATP, and dNTPs with different labels. Walt et al also teach a composition comprising a substrate with discrete sites (wells) and a population of microspheres randomly distributed in the wells, the microspheres comprising a bioactive agent (claims 1, 5, 9, 27 and 39), but does not teach dNTPs, a second enzyme for conversion of PPi to ATP, a third enzyme for the detection of ATP, and dNTPs with different labels.

C) Nyren et al. teach a kit comprising a sequencing primer, a polymerase, a detection enzyme means for identifying pyrophosphate release, dNTPs or ddNTPs (page 20, second paragraph; page 21, first paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have added kits of Nyren et al. to a kit and a composition disclosed by Navot et al. and Walt et al. The motivation to do so would have been that kits were conventional in the field of molecular biology and provided the benefits of convenience and cost-effectiveness for practitioners in the art.

9. No claims are allowed.

Conclusion

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gary Benzion will move to the new office on January 22, 2004. His new phone number is (571) 272-0782.

TS
January 15, 2004

JEFFREY FREDMAN
PRIMARY EXAMINER